IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

In re: Rosuvastatin Calcium Patent Litigation	Civ. No. 08-md-1949 **REDACTED VERSION DI 283**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Mylan Pharmaceuticals Inc., Defendant.	Civ. No. 07-805-JJF-LPS **REDACTED VERSION DI 180**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Sun Pharmaceutical Industries Ltd., Defendant.	Civ. No. 07-806-JJF-LPS **REDACTED VERSION DI 182**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Sandoz Inc., Defendant.	Civ. No. 07-807-JJF-LPS **REDACTED VERSION DI 198**

AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Par Pharmaceutical, Inc., Defendant.	Civ. No. 07-808-JJF-LPS **REDACTED VERSION DI 177**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Apotex Inc. and Apotex Corp., Defendants.	Civ. No. 07-809-JJF-LPS **REDACTED VERSION DI 202**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Aurobindo Pharma Ltd. and Aurobindo Pharma USA Inc., Defendants.	Civ. No. 07-810-JJF-LPS **REDACTED VERSION DI 238**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Cobalt Pharmaceuticals Inc. and Cobalt Laboratories Inc., Defendants.	Civ. No. 07-811-JJF-LPS **REDACTED VERSION DI 202**

AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Aurobindo Pharma USA Inc. and Aurobindo Pharma Limited Inc., Defendants.	Civ. No. 08-359-JJF-LPS **REDACTED VERSION DI 159**
AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha, Plaintiffs, v. Teva Pharmaceuticals USA Defendants.	Civ. No. 08-426-JJF-LPS **REDACTED VERSION DI 165**

DECLARATION OF MARY W. BOURKE IN SUPPORT OF PLAINTIFFS' MOTION FOR SUMMARY JUDGMENT OF NO INEQUITABLE CONDUCT

1. My name is Mary W. Bourke, an attorney of record representing Plaintiffs AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, IPR Pharmaceuticals Inc., and Shionogi Seiyaku Kabushiki Kaisha in the above-referenced actions. I have personal knowledge of the documents identified herein.

2. Attached hereto as Exhibit 1 is a Statement of Undisputed Facts.

3. Attached hereto as Exhibit 2 is a true and correct copy of United States Reissue Patent No. RE37,314.

4. Attached hereto as Exhibit 3 is a true and correct copy of excerpts from the deposition transcript of Dr. Haruo Koike.

5. Attached hereto as Exhibit 4 is a true and correct copy of excerpts from the deposition transcript of Ms. Tomoko Ozawa (formerly known as Ms. Tomoko Kitamura).

[redacted] Attached hereto as Exhibit 5 is a true and correct copy of [redacted]

[redacted] Attached hereto as Exhibit 6 is a [redacted]

[redacted] Attached hereto as Exhibit 7 is [redacted]

[redacted] Attached hereto as Exhibit 8 is a [redacted]

10. Attached hereto as Exhibit 9 is a true and correct copy of correspondence to Vossius & Partner Patentanwaelte ("Vossius") dated May 28, 1992 and bearing Bates Stamp No. SH00058590.

11. Attached hereto as Exhibit 10 is a true and correct copy of correspondence to Wenderoth, Lind & Ponack ("Wenderoth") dated May 28, 1992 and bearing Bates Stamp No. SH00088805-10.

12. Attached hereto as Exhibit 11 is a true and correct copy of correspondence from Wenderoth dated June 12, 1992 and bearing Bates Stamp No. SH00088814-19.

13. Attached hereto as Exhibit 12 is a true and correct copy of excerpts from the deposition transcript of Mr. Takashi Shibata.

14. Attached hereto as Exhibit 13 is a true and correct copy of excerpts from the deposition transcript of Ms. Masako Washio (formerly known as Ms. Masako Shimizu).

15. Attached hereto as Exhibit 14 is a true and correct copy of correspondence from Vossius dated October 14, 1992, enclosing a European Search Report, and bearing Bates Stamp No. SH00088308-11 and a certified translation thereof.

16. Attached hereto as Exhibit 15 is a true and correct copy of correspondence from Vossius dated March 20, 1996, enclosing a first Official Communication from the European Patent Office, and bearing Bates Stamp No. SH00088387-91.

17. Attached hereto as Exhibit 16 is a true and correct copy of excerpts from the deposition transcript of Mr. Katsuhiko Tamaki.

18. Attached hereto as Exhibit 17 is a true and correct copy of an Office Action issued by the United States Patent & Trademark Office ("USPTO") dated September 2, 1992 and bearing Bates Stamp No. SH00088827-29.

19. Attached hereto as Exhibit 18 is a true and correct copy of correspondence to Wenderoth dated December 2, 1992 and bearing Bates Stamp No. SH00088831-42.

20. Attached hereto as Exhibit 19 is a true and correct copy of an Office Action issued by the USPTO dated January 8, 1993 and bearing Bates Stamp No. SH00088858-62.

21. Attached hereto as Exhibit 20 is a true and correct copy of correspondence to Wenderoth dated March 9, 1993 and bearing Bates Stamp No. SH00088869-71.

[redacted] Attached hereto as Exhibit 21 is a true and correct copy of a [redacted]

[redacted] Attached hereto as Exhibit 22 is a [redacted]

24. Attached hereto as Exhibit 23 is a true and correct copy of a document dated January 21, 1993 and bearing Bates Stamp No. SH00059692 and a certified translation thereof.

[redacted] Attached hereto as Exhibit 24 is a [redacted]

26. Attached hereto as Exhibit 25 is a true and correct copy of a Reissue Declaration bearing Bates Stamp No. AZ01050371-73.

27. Attached hereto as Exhibit 26 is a true and correct copy of an Information Disclosure Statement and Form PTO 1449 bearing Bates Stamp No. AZ01050352-64.

Ford F. Farabow Charles E. Lipsey Kenneth M. Frankel York M. Faulkner FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P. 901 New York Avenue, N.W. Washington, D.C. 20001 Telephone: (202) 408-4000 Facsimile: (202) 408-4400 Henry J. Renk FITZPATRICK, CELLA, HARPER & SCINTO 1290 Avenue of the Americas New York, NY 10104-3800 Telephone: (212) 218-2100 Facsimile: (212) 218-2200 *Of Counsel for Plaintiffs* Dated: September 11, 2009 Redacted Version Filed : September 18, 2009	Respectfully Submitted: */s/ Mary W. Bourke* Mary W. Bourke (#2356) CONNOLLY BOVE LODGE & HUTZ LLP 1007 N. Orange Street P.O. Box 2207 Wilmington, DE 19899 Telephone: (302) 658-9141 Facsimile: (302) 658-5614 mbourke@cblh.com *Attorneys for Plaintiffs* Thomas A. Stevens (#3039) ASTRAZENECA PHARMACEUTICALS LP 1800 Concord Pike Wilmington, DE 19850-5437 (302) 885-5457 (302) 886-8037 *Attorney for AstraZeneca Pharmaceuticals LP, AstraZeneca UK Limited, and IPR Pharmaceuticals*

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EXHIBIT 1

STATEMENT OF UNDISPUTED FACTS

1. In the early 1990's, Dr. Kentaro Hirai, Teruyuki Ishiba, Dr. Haruo Koike, and Masamichi Watanabe (the "Hirai Group")—the inventors named on the '314 patent—discovered rosuvastatin, a chemical compound with a "pyrimidine" core, which is now the active ingredient in Crestor®. (Ex. 2.)

[redacted]

5. [redacted]: (1) G. Beck et al., J. Med. Chem., 33, 52-60 (1990) and (2) B. Roth et al., J. Med. Chem., 34, 463-466 (1991). (Ex. 6.) Neither article discloses rosuvastatin.

6. [redacted] filed the Japanese application in July 1991. (Ex. 7 at 3.)

[redacted]

[redacted]

15. An ESR issued during the prosecution of the European patent application for the Hirai Group's pyrimidine compounds. The EPO located EPA 0 367 895 (Sandoz) and sent an ESR to Shionogi's European counsel, Vossius. The ESR identified the Sandoz prior art reference as an "X" reference (particularly relevant if taken alone). (Ex. 14.) The ESR did not require a response and no substantive prosecution of the European patent application occurred until 1996. (*Id.* & Ex. 15.)

[redacted]

[redacted]

20. There were only two formal rejections to the claims in the U.S. application, neither dealing with prior art. The rejections were based on the USPTO's assertion that the scope of the claims was not supported by the written description of the invention provided in the patent's specification. [redacted]

21. [redacted] retained responsibility for and handled all substantive prosecution in the U.S. application until the '440 patent issued on November 9, 1993. (*See Id.* & Ex. 2.) No prior art issues were raised during this prosecution.

22. With no knowledge of the prior art or the ESR, Mr. Jacob did not file an IDS disclosing that art to the USPTO.

[redacted]

[redacted]

***

[redacted]

[redacted]

28. [redacted]

29. In 1998, Shionogi filed an application with the USPTO to reissue the `440 patent. The application stated that the reissue was necessary because of an error in the `440 patent, it claimed more than Shionogi had a right to claim in view of the Sandoz prior art. Shionogi stated that the error was not the result of deceptive intent. (Ex. 25.)

30. During the `314 patent prosecution, Shionogi submitted following references to the USPTO for consideration: (1) U.S. Patent No. 4,868,185 (Chucholowski); (2) U.S. Patent No. 5,925,852 (Kesseler et al.); (3) U.S. 5,026,708 (Nissan); (4) EP 0 330 057 (Bayer); (5) EP 0 367 895 (Sandoz); (6) G. Beck et al., J. Med. Chem., 33, 52-60 (1990); and (7) B. Roth et al., J. Med. Chem., 34, 463-466 (1991). (Ex. 26.)

EXHIBIT 2

US00RE37314E

(19) **United States**

(12) **Reissued Patent**

Hirai et al.

(10) **Patent Number: US RE37,314 E**

(45) **Date of Reissued Patent: Aug. 7, 2001**

(54) **PYRIMIDINE DERIVATIVES**

(75) Inventors: **Kentaro Hirai**, Kyoto; **Teruyuki Ishiba**, Osaka; **Haruo Koike**, Kyoto; **Masamichi Watanabe**, Shiga, all of (JP)

(73) Assignee: **Shionogi Seiyaku Kabushiki Kaisha**, Osaka (JP)

(21) Appl. No.: **09/141,731**

(22) Filed: **Aug. 27, 1998**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,260,440**
Issued: **Nov. 9, 1993**
Appl. No.: **07/897,793**
Filed: **Jun. 12, 1992**

(30) **Foreign Application Priority Data**

Jul. 1, 1991 (JP) 3-188015

(51) **Int. Cl.**[7] **A61K 31/505**; C07D 239/34; C07D 239/38; C07D 239/42

(52) **U.S. Cl.** **514/316**; 544/318; 544/322

(58) **Field of Search** 514/756; 544/297

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,868,185 9/1989 Chucholowski et al. 514/256
4,925,852 5/1990 Kesseler et al. 514/256
5,026,708 6/1991 Fujikawa et al. 514/256

FOREIGN PATENT DOCUMENTS

0 330 057 8/1989 (EP) .
0 367 895 5/1990 (EP) .

OTHER PUBLICATIONS

Moore et al, J. Am. Chem. Soc., vol. 107, pp. 3694–3701, 1985.*

G. Beck et al., *J. Med. Chem.*, 33, 52–60 (1990).

B. Roth et al., *J. Med. Chem.*, 34, 463–466 (1991).

* cited by examiner

Primary Examiner—Richard L. Raymond

(74) *Attorney, Agent, or Firm*—Pillsbury Madison & Sutro, LLP Intellectual Property Group

(57) **ABSTRACT**

The compounds of the present invention inhibit the HMG-CoA reductase, and subsequently suppress the biosynthesis of cholesterol. And they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

3 Claims, No Drawings

PYRIMIDINE DERIVATIVES

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This application is a reissue of U.S. Pat. No. 5,260,440, issued Nov. 8, 1993.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor.

2. Prior Art

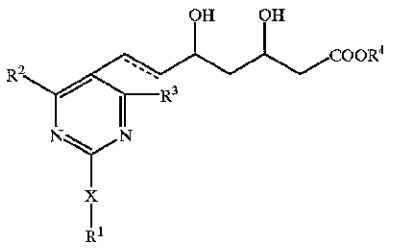
As the first generation of drugs for the treatment of atherosclerosis by inhibiting the activity of HMG-CoA reductase, there are known Mevinolin (U.S. Pat. No. 4,231,938), pravastatin sodium (U.S. Pat No. 4,346,227), and, simvastatin (U.S. Pat. No. 4,444,784), which are fungal metabolites or of the chemical modifications. Recently, synthetic inhibitors of HMG-CoA reductase such as fluvastatin (F. G. Kathawala et al., 8th Int'l Symp. on Atherosclerosis, Abstract Papers, p. 445, Rome (1988)) and BMY 22089 (GB Pat. No. 2,202,846) are developed as the second generation drugs.

SUMMARY OF THE INVENTION

The compounds of the present invention inhibit the HMG-CoA reductase, which plays a main role in the synthesis of cholesterol, and subsequently they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of hypercholesterolemia, hyperlipoproteinemia, and atherosclerosis.

DETAILED DESCRIPTION

The present invention relates to compounds of the formula (I):



wherein R^1 is lower alkyl, aryl or aralkyl, each of which may have one or more substituents: R^2 and R^3 each is independently hydrogen, lower alkyl, or aryl, and each of said lower alkyl and aryl may have one or more substituents; R^4 is hydrogen, lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may have a stubstituent; the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone. This invention also provides a pharmaceutical composition comprising the same.

In the specification, the term "lower alkyl" refers to a straight, branched, or cyclic C_1 to C_6 alkyl, including methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, cyclobutyl, n-pentyl, isopentyl, neopentyl, tert-pentyl, cyclopentyl, n-hexyl, and

isohexyl and the like. Further, the lower alkyl may be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano. Halogen means fluorine, chlorine, bromine and iodine.

The term "aryl" refers to C_6 to C_{12} aromatic group including phenyl, tolyl, xylyl, biphenyl, naphthyl, and the like. The aryl may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano. Preferred aryl is phenyl substituted by 1 to 3 halogens.

The term "aralkyl" refers to C_1 to C_6 lower alkyl substituted by C_6 to C_{12} aromatic aryl group defined above. Examples of them are benzyl, phenethyl, phenylpropyl and the like, each of which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl halogen, amino, cyano, and the like.

The term "a cation capable of forming a non-toxic pharmaceutically acceptable salt" refers to alkali metal ion, alkaline earth metal ion, and ammonium ion. Examples of alkali metal are lithium, sodium, potassium, and cesium, and examples of alkaline earth metal are beryllium, magnesium, and calcium. Especially, sodium and calcium are preferred.

Examples of "acyl" are formyl acetyl, propionyl, butyryl, isobutyryl, valeryl, and isovaleryl.

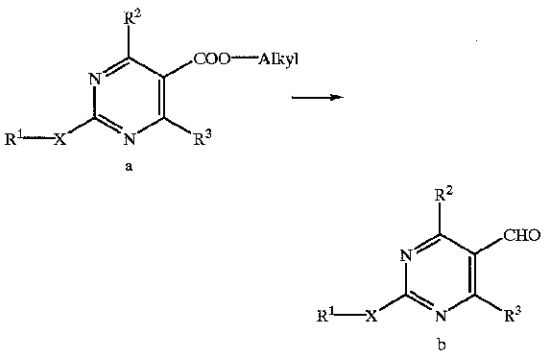
In the term "imino which may have a substituent", preferred substituents are acyl, optionally substituted amino, and substituted sulfonyl.

The term "substituted amino as substituent" means amino group substituted by sulfonyl and alkylsulfonyl. Examples of them are sulfonyl amino and methanesulfonyl amino.

The term "substituted sulfonyl as substituent" means sulfonyl group substituted by alkyl, amino, or alkylamino. Examples of them are methanesulfonyl, sulfamoyl, methylsulfamoyl, and N-methylsulfamoyl.

The compounds of the present invention can be prepared by the following method.

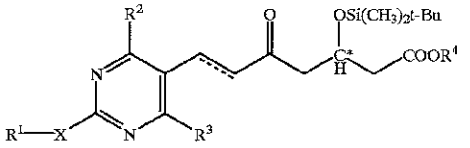
(1) The carboxylate group of the compound a is converted into the alcohol group by the reduction in an appropriate inactive solvent such as THF, ether, and toluene in the presence of the reductant such as LiAlH and DIBAL-H. The reaction is performed at −70° to 50° C., preferably at near room temperature, for 10 minutes to 10 hours, preferably for 30 minutes to 3 hours. Then the obtained alcohol is subjected to oxidation in an appropriate solvent such as methylene chloride in the presence of the oxidizing agent such as TPAP/4-methylmorpholin-N-oxide or pyridium chlorochromate to give aldehyde compound b. The reaction is performed at 0°–60° C., preferably at near room temperature, for 10 minutes to 10 hours, preferably 30 minutes to 3 hours.



wherein R^1, R^2, and R^3 each has the same meaning as defined above, and Alkyl means lower alkyl.

(2) The obtained compound b is subjected to reaction with (3R)-or (3S)-3-(tert-butyldimethylsilyloxy-5-oxo-6-triphenylphosphoranylidene hexanoic acid derivatives in an appropriate solvent such as acetonitrile, diethylether, tetrahydrofuran, and dimethylformamide to give the compound c. The reaction is performed for 1–30 hours, preferably for 10–15 hours under heating.

c



wherein C* means asymmetric carbon atom, the dotted line means the presence or absence of the double bond, R^1, R^2, R^3, and R^4each has the same meaning as defined above.

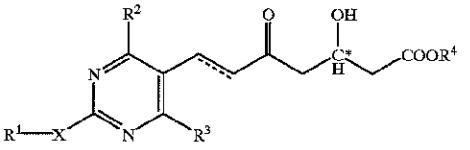
(3) The compound c is subjected to elimination of the tertbutyldimethylsilyl group in an appropriate organic solvent in the presence of hydrogen halogenide to give the compound d.

Every sort of halogen can be used for hydrogen halogenide. Amongst all, hydrogen fluoride is preferred.

The same organic solvents as used in the step (2) may be employed. Acetonitrile is especially preferred.

The reaction is performed in a range of from 0° to 60° C., preferably at room temperature, for 0.5–10 hours, preferably for 1–2 hours.

d



wherein C*, the dotted line, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.

(4) The compound d is reacted with diethylmethoxyborane and $NaBH_4$ in an alcohol-organic solvent mixture and subjected to column chromatography of silica gel to give the compound (I) (in case R^4 is lower alkyl). The reaction is performed at a temperature between −100° to 20° C., preferably between −85° to −70° C. under cooling, for 10 minutes to 5 hours, preferably for 30 minutes to 2 hours.

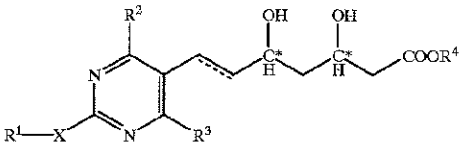
Here, the alcohol includes methanol, ethanol, propanol, and butanol; and the organic solvent includes the same as in the step (3).

Further, if necessary, the obtained compound may be subjected to saponification with the solution of metalic hydroxide (R^4: cation), and after the saponification, the reaction mixture is neutralized with an acid and extracted with an organic solvent (R^4: hydrogen). The saponification is performed in a popular solvent such as water, acetonitrile, dioxane, acetone, and the mixture thereof, preferably in the presence of a base, by a conventional method. The reaction is performed at 0° to 50° C., preferably at near room temperature.

As metalic hydroxide which may be used are sodium hydroxide, potassium hydroxide, and their analogue.

Acids which may be used include inorganic acids such as hydrochloric acid, sulfuric acid and the like.

(I)



wherein C*, the dotted line, R^1, R^2, R^3, and R^4 each has the same meaning as defined above.

Further, if necessary, the obtained compounds (I) are subjected to reflux under heating to give the corresponding lactones.

The compound of the present invention can be administered orally or parenterally. For example, the compound of the present invention may be orally administered in the form of tablets, powders, capsules and granules, aqueous or oily suspension, or liquid form such as syrup or elixir, and parenterally in the form of aqueous or oily suspension.

These preparations can be prepared in a conventional manner by using excipients, binders, lubricants, aqueous or oily solubilizers, emulsifier, suspending agents, and the like. And preservatives and stabilizers can be further used.

The dosages may vary with the administration route, age, weight, condition, and the kind of disease of the patients, but are usually 0.5–200 mg/day, preferably 1–100 mg/day through oral route, and 0.1–100 mg/day, preferably 0.5–50 mg/day through parenteral route. They may be used in a single or divided doses.

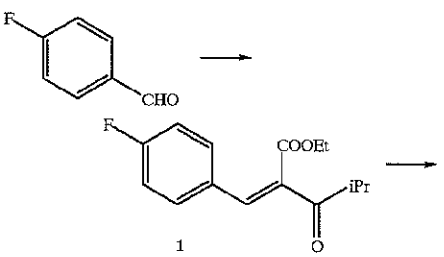
The present invention is illustrated by the following examples and reference examples, which are not to be considered as limiting.

The abbreviations used in examples and reference examples have the following meanings.

Me: methyl,
Et: ethyl,
i-Pr: isopropyl
t-Bu: tert-butyl,
Ph: phenyl,
DMF: dimethylformamide,
THF: tetrahydrofuran
DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
TPAP: tetrapropylammonium perruthenate
HMPA: hexamethylphosphoramide
DIBAL-H: diisobutylaluminum hydride.

REFERENCE EXAMPLE 1

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylthiopyrimidine-5-carboxylate (III-1) and
Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonylpyrimidine-5-carboxylate (III-2)



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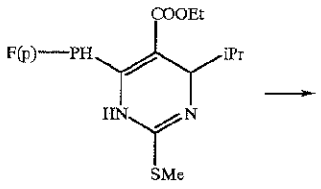
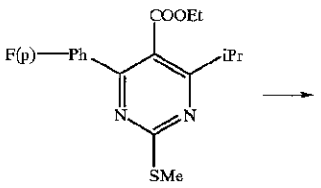
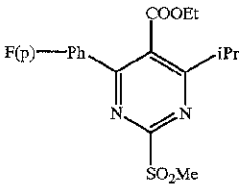


2



(III-1)



(III-2)

p-Fluorobenzaldehyde 81.81 g is reacted in the same manner as disclosed in the specification of JP Unexamed. Pat. Publn. No. 61-40272 to give 151.0 g (Yield: 86.7%) of the compound 1. Then the mixture of a solution of 44.68 g of the compound 1 in 65 ml of HMPA and 28.24 g of s-methylisourea hydrogen sulfate is stirred at 100° C. for 22 hours. Then the reaction mixture is extracted with ether, and washed with saturated sodium hydrogencarbonate and water in order. The organic layer is dried, and the solvent is distilled away. The obtained residue is subjected to column chromatography of silica gel to give 26.61 g (yield: 46.8%) of the compound 2.

To a solution of the obtained compound 2 in 400 ml of benzene is added 21.64 g (0.095 mmol) or DDQ, and the mixture is stirred for 30 minutes. Then the mixture is subjected to column chromatography of silica gel to give 24.31 g (Yield: 91.9%) of the compound (III-1).

NMR ($CDCl_3$) δ: 1.10 (t, J=7,3H): 1.31 (d, J=7,6 Hz); 2.61 (s, 3H); 3.18 (hept, J=7,1H); 4.18 (q, J=7,2H); 7.12 (m, 2H), 7.65 (m, 2H).

To a solution of 13.28 g (0.04 mmol) of the compound (III-1) in chloroform is added 17.98 g of m-chloroperbenzoic acid, and the reaction mixture is stirred at room temperature. Then it is washed with sodium sulfate and saturated sodium hydrogencarbonate in order. The solution is dried, and the solvent is distilled away and washed with n-hexane to give 13.93 g (Yield 95.7%) of the compound (III-2).

NMR ($CDCl_3$) δ: 1.16 (t, J=7,3H); 1.37 (d, J=7,6H); 3.26 (hept, J=7,1H); 3.42 (s, 3H), 4.28 (q, 2H); 7.18 (m, 2H); 7.76 (m, 2H).

REFERENCE EXAMPLE 2

Another synthetic method of the compound (III-1)

To a solution of 200 mg (0.594 mmol) of the compound 2 in 5 ml of dichloromethane are added 0.5 g (6.10 equivalent) of potassium carbonic anhydride and 166 mg (1.1 equivalent) of iodine, and the mixture is stirred at room temperature for 2.5 hours. After reaction, to the mixture is added saturated sodium hydrogensulfite and extracted with ether. The organic layer is washed with water and dried. The solvent is distilled away under reduced pressure to give 166 mg (Yield: 83.6%) of the compound (III-1) as resinous substance.

NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7); 1.31 (d, 6H, J=7); 2.61 (s, 3H) 3.17 (heptet, 1H, J=7); 4.18 (q, 2H, J=7); 7.07–7.17 (m, 2H); 7.61–7.69 (m, 2H)

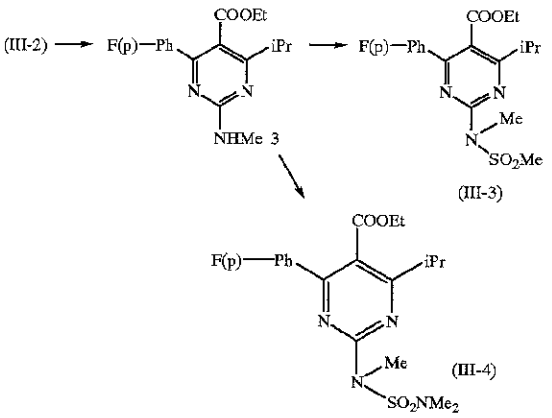
REFERENCE EXAMPLE 3

Another synthetic method of the compound (III-2)

To a solution of 1.0 g (2.97 mmol) of the compound 2 in 10 ml of acetone is added 1.5 g (9.48 mmol) of potassium permanganate, and the mixture is stirred at room temperature for 15 minutes. Acetic acid 1.0 ml is added thereto, and the mixture is stirred at room temperature for further 30 minutes and water is added thereto. The reaction mixture is extracted with ether, washed with saturated sodium hydrogencarbonate and saturated brine and dried over anhydrous magnesium sulfate. The solvent is distilled away under reduced pressure to give 1.07 g (2.94 mmol) (Yield: 99.1%) of the compound (III-2) as crystals.

REFERENCE EXAMPLE 4

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl-sulfonylamino)pyrimidine-5-carboxylate (III-3) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-dimethylsulfamoylamino)pyrimidine-5-carboxylate (III-4)



To a solution of 52.7 g (144 mmol) of the compound (III-2) in 500 ml of absolute ethanol is added gradually a solution of 71.9 ml of 5N methylamine in ethanol under ice-cooling. The reaction mixture is warmed to room temperature, stirred for 1 hour and evaporated under reduced pressure. To the residue is added water, and the mixture is extracted with ether, dried and evaporated under reduced pressure to give 46.9 g (Yield: 100%) of the compound 3. mp. 85°–86° C.

Anal Calcd. (%) for $C_{17}H_{20}N_3FO_2$: C,64.34; H,6.35; N,13.24: F,5.99. Found: C,64.42, H,6.46: N,13.30; F,6.14.

To a solution of 370 mg (1.213 mmol) of the compound 3 in 5 ml of DMF is added 60 mg of 60% NaH under ice-cooling, and the reaction mixture is stirred for 30 min-

utes. Methanesulfonyl chloride 208 mg is added thereto, and the mixture is warmed to room temperature and stirred for 2 hours further. To the mixture is added ice-water, and the mixture is extracted with ether. The organic layer is washed with water and dried. The solvent is evaporated under reduced pressure, and the resulting residue is washed with ether-n-pentane to give 322 mg (Yield: 57.6%) of the compound (III-3).

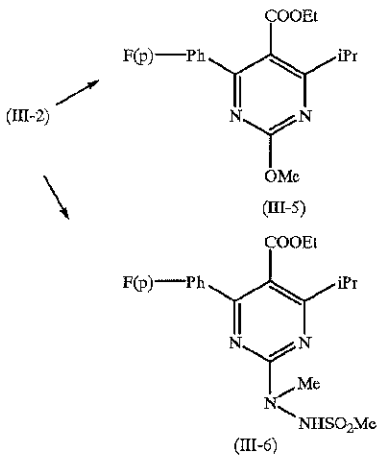
NMR ($CDCl_3$) δ: 1.10 (t, J=7,3H); 1.32 (d, J=7,6H); 3.24 (hept,J=7,1H); 3.52 (s,3H); 3.60 (s, 3H); 4.19 (q, J=7,2H); 7.14 (m, 2H); 7.68 (m, 2H).

To a solution of 4.13 g (13.0 mmol) of the compound 3 in 40 ml of DMF is added 0.57 g of 60% NaH under ice-cooling, and the mixture is warmed to room temperature and stirred for 1 hours. After cooling again, dimethylsulfamoyl chloride 2.43 g (16.9 mmol) is dropwise added thereto, and the mixture is stirred for 2.5 hours. To the mixture is added icewater, and the mixture is extracted with ether washed with water, dried and evaporated under reduced pressure to distill ether. The resulting residue is washed with ether-hexane to give 4.10 g (Yield: 74.2%) of the compound (III-4). mp. 114°–116° C.

Anal Calcd. (%) for $C_{19}H_{25}N_4SFO_4$: C,53.76; H,5.94; N,13.20; F,4.48. Found: C,53.74: H,5.96; N,13.19; F,4.78.

REFERENCE EXAMPLE 5

Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-methoxypyrimidine-5-carboxylate (III-5) and Ethyl 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylhydrazino)pyrimidine-5-carboxylate (III-6)



To a solution of 1.39 g (3.8 mmol) of the compound (III-2) in 60 ml of absolute methanol is added a solution of 0.41 g (7.6 mmol) of sodium methoxide under ice-cooling. The reaction mixture is warmed to room temperature gradually and stirred for 1 hour. The mixture is neutralized with acetic acid and extracted with ether. The organic layer is washed with sodium bicarbonate and water in order, dried and evaporated under reduced pressure to distill ether. The residue is subjected to column chromatography of silica gel to give 1.17 g (Yield: 96.7%) of the compound (III-5).

NMR ($CDCl_3$) δ: 1.10 (t, 3H, J=7 Hz); 1.32 (d, 6H, J=6.6 Hz); 3.21 (m, 1H); 4.08 (s, 3H); 4.18 (q, 2H, J=7 Hz); 7.07–7.74 (m, 4H).

To a solution of 2.50 g (6.77 mmol) of the compound (III-2) in 50 ml of absolute ethanol is added 0.80 g (16.93 mmol) of methyl hydrazine under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 2 hours and extracted with ether. The organic layer is washed with saturated brine and dried to distill the solvent. To a mixture of 2.37 g of the thus obtained compound and a mixture of anhydrous THF and anhydrous pyridine is added 1.03 g (7.84 mmol) of methanesulfonyl chloride under testing. The reaction mixture is warmed to room temperature and stirred for 1.5 hours. To the mixture are added 3 ml of anhydrous pyridine and 1.53 g (11.65 mmol) of methanesulfonyl chloride, and the mixture is stirred for 2 hours. To the reaction mixture is added ice-water and extracted with ether. The organic layer is washed with water and the resulting oily residue is subjected to column chromatography of silica gel to give 2.75 g (Yield: 94.0%) of the compound (III6).

NMR ($CDCl_3$) δ: 1.08 (t, J=7,3H); 1.29 (d, J=7,6H); 2.96 (s, 3H); 3.24 (hept, J=7,1H); 3.59 (s, 3H); 4.16 (q, J=7,2H); 7.14 (m, 2H), 7.63 (m, 2H).

REFERENCE EXAMPLE 6

Methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate

(1) (3R)-3-(tert-butyldimethylsilyloxy)glutaric acid-1-((R)-(–)mandelic acid ester*1 65 g (164 mmol) is dissolved into 60 ml of methanol, a solution of sodium methoxide in methanol (28% methanol 310 ml, 1.6 mol) is added dropwise thereto under nitrogen atmosphere at 0° C. for 45 minutes at internal temperature under 7° C. The reaction mixture is stirred at 0° C. for 30 minutes and poured into a mixture of 150 ml of conc.HCl, 300 ml of water, and 500 ml of methylene chloride being stirred under ice-cooling and the organic layer is collected. The aqueous layer is extracted with 200 ml of methylene chloride, and each organic layer is washed with dil.HCl and brine in order. Each organic layer are collected and dried over anhydrous magnesium sulfate and evaporated to distill the solvent to give half ester compound.

*1: This compound can be prepared by the method described at page 10 in the specification of KOKAI 2-250852.

^{1}HNMR($CDCl_3$) δ: 0.08 (s, 3H); 0.09 (s, 3H); 0.86 (s, 9H); 2.52–2.73 (m, 4H); 3.08 (s, 3H); 4.55 (quint, 1H, J=6Hz).

IR ($CHCl_3$): 2880, 1734, 1712, 1438, 1305, 1096, 836 cm^{-1}.

[α]D=–5.0±0.4° (C=1.04, 23.5° C., $CHCl_3$).

Rf 0.32 ($CHCl_3$/MeOH=9/1).

(2) To a solution of the thus obtained half ester compound in 10 ml of ether are added dropwise triethylamine and ethyl chlorocarboxylate in order under nitrogen atmosphere at –78° C. The resulting white suspension is stirred at 0° C. for 1 hour and cooled to –78° C. The resulting precipitate is filtered under nitrogen atmosphere and the filtrate is washed with 15 ml of ether. To a suspension of 1.29 g (3.6 mmol) of methyl bromide triphenylphosphonium in 5 ml of THF is added dropwise butyllithium (1.6M hexane, 2.25 ml, 3.6 mmol) under nitrogen atmosphere at –78° C. The reaction mixture is stirred at 0° C. for 1 hour and cooled to –78° C. and added dropwise to the solution of thus obtained active ester compound in ether. The reaction mixture is washed with 5 ml of THF and stirred at 0° C. for 1 hour, and 10 ml of 5% sodium hydrogencarbonate is added thereto. The reaction mixture is stirred for 5 minutes and extracted with ethyl acetate and the organic layer is separated and the

remaining aqueous layer is extracted with ethyl acetate. Each organic layer is collected and washed with brine, dried over anhydrous magnesium sulfate and concentrated. The obtained residue is subjected to column chromatography of silica gel eluting with ether-ethyl acetate and crystallized from ether-hexane to give objective compound.

^{1}HNMR ($CDCl_3$)δ: 0.04 (s, 3H); 0.06 (s, 3H); 0.83 (s, 9H); 2.4–2.9 (m, 4H); 3.64 (s, 3H); 3.74 (d, 1H); 4.5–4.7 (m, 1H); 7.4–7.8 (m, 15H).

IR ($CHCl_3$): 2380, 1730, 1528, 1437, 1250, 1106, 835 cm^{-1}.

[α]D=−6.2° (C=1.27, 22.0° C., $CHCl_3$).

mp.:77.5°–78.5° C., Rf=0.48 ($CHCl_3$/MeOH=9/1).

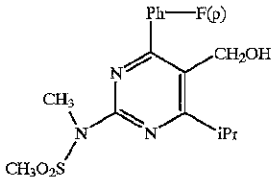
Anal Calcd. (%) for $C_{31}H_{39}O_4PS$: C, 69.63; H,7.35; P,5.79. Found: C, 69.35; H,7.35; P,6.09.

EXAMPLE 1

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I a-1)

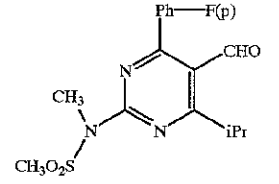
(1) To a solution of 322 mg of the compound (III-3) obtained in Reference Example 2 in 7 ml of anhydrous toluene is added dropwise 1.4 ml of DIBAL-H in 1.5M toluene at −74° C., and the reaction mixture is stirred for 1 hour and acetic acid is added thereto. The mixture is extracted with ether, and the organic layer is washed with sodium bicarbonate and water, dried and evaporated under reduced pressure to distil ether. The obtained residue is subjected to column chromatography of silica gel eluting with methylene chloride/ether (20/1) to give 277 mg (Yield: 96.1%) of [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]methanol 4.

4



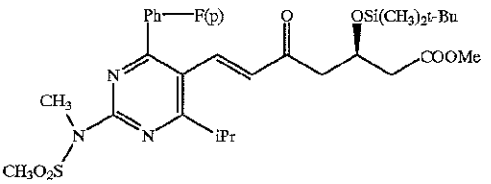
(2) A suspension of 277 mg of the thus obtained compound 4, 190 mg of 4-methylmorpholin-N-oxide, 6 mg of TPAP, 1.0 g of powder molecular sieve 4A, and 10 ml of methylene chloride is stirred for 2 hours. The insoluble matter is filtered off and the two-thirds of the filtrate is distilled away under reduced pressure. The resulting residue is subjected to column chromatography of silica gel eluting with methylene chloride to give 196 mg (Yield: 71.2%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidinecarbardehyde as crystals.

5



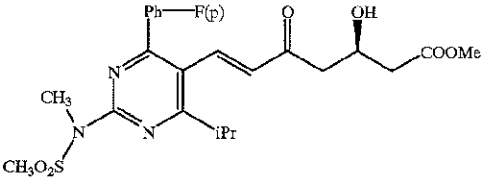
(3) A solution of 190 mg of the compound 5, 450 mg of methyl (3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate (Reference Example 6), and 5 ml of acetonitrile is refluxed under heating for 14 hours and evaporated under reduced pressure to distill acetonitrile. The resulting residue is subjected to column chromatography of silica gel eluting with methylene chloride to give 233 mg (Yield: 71.3%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R)-3-(tert-butyldimethylsilyloxy)-5-oxo-(E)-6-heptenate 6 as syrup.

6



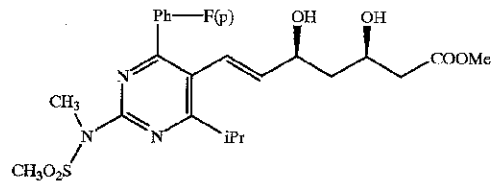
(4) To a solution of 16 g of the compound 6 in 100 ml of acetonitrile is added dropwise a solution of 48% hydrogen flouride in 400 ml of acetonitrile (1:19) under ice-cooling, and the mixture is warmed to room temperature and stirred for 1.5 hours. The reaction mixture is neutralized with sodium bicarbonate and extracted with ether. The organic layer is washed with sodium chloride, dried and evaporated under reduced pressure to distil ether to give 13 g (Yield: 100%) of methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R)-3-hydroxy-5-oxo-(E)-6-heptenate 7 as syrup.

7



(5) To a solution of 13 g of the compound 7 in 350 ml of anhydrous THF and 90 ml of methanol is added a solution of 29.7 ml of 1M diethylmethoxyborane-THF at −78° C., and the mixture is stirred at the same temperature for 30 minutes. To the mixture is added 1.3 g of $NaBH_4$, and the mixture is stirred for 3 hours. Acetic acid 16 ml is added thereto, and the mixture is adjusted to pH 8 with saturated sodium bicarbonate and extracted with ether. The organic layer is washed with water, dried and evaporated ether under reduced pressure. To the resulting residue is added methanol and the mixture is evaporated under reduced pressure for three times. The resulting residue is subjected to column chromatography of silica gel eluting with methylene chloride/ether (3/1) to give 11.4 g (Yield: 85.2%) of methyl 7-[4-(4-fluorophenyl)-6-iso-propyl-2-methyl-N-methylsulfonylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate as syrup.

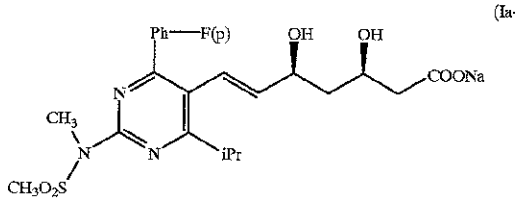
(Ib-1)



NMR ($CDCl_3$) δ: 1.27 (d, J=7,6H); 1.53 (m, 2H); 2.47 (d, J=6,2H); 3.36 (hept, J=2H); 3.52 (s, 3H); 3.57 (s, 3H); 3.73 (s, 3H); 4.20 (m, 1H); 4.43 (m, 1H); 5.45 (dd, J=5,16, 1H); 6.64 (dd, J=2,16, 1H); 7.09 (m, 2H); 7.64 (m, 2H).

(6) To a solution of 11.4 g of the compound (I b-1) in 160 ml of ethanol is added 223 ml of 0.1N sodium hydroxide under ice-cooling. The reaction mixture is warmed to room temperature and stirred for 1 hour. The solvent is distilled away under reduced pressure, and ether is added to the resulting residue and the mixture is stirred to give 11.0 g (Yield: 95.0%) of the objective compound (I a-1) as powdery crystals.

(Ia-1)



$[\alpha]_D$=+18.9±0.6° (C=1.012, 25.0° C., H_2O).

NMR ($CDCl_3$) δ: 1.24 (d, J=7,6H); 1.48 (m, 1H); 1.65 (m, 1H); 2.27 (dd,J=2,6.2H); 3.41 (hept, J=7,1H); 3.48 (s, 3H); 3.59 (s, 3H); 3.73 (m, 1H); 4.32 (m 1H); 5.49 (dd, J=7,16 1H); 6.62 (d, J=16,1H); 7.19 (m, 2H); 7.56 (m, 2H).

EXAMPLE 2

Sodium (+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylamino)pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I a-2)

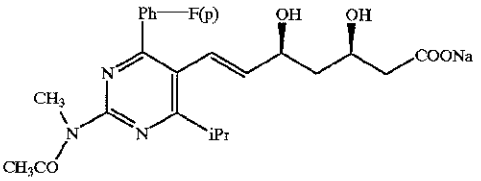
(1) Ethyl 4-(4-fluorophenyl-6-isopropyl-2-methylaminopyrimidine-5-carboxylate 3 838 mg obtained in Reference Example 4 is allowed to react in the same manner as in Example 1 (1) and (2) to give 157 mg of 4-(4-fluorophenyl)-6-isopropyl-2-methylaminopyrimidine-5-carbaldehyde.

(2) A solution of 157 mg of thus obtained aldehyde compound in 4 ml of anhydrous DMF is reacted with 25 mg of 60% NaH under ice-cooling for 30 minutes, 0.05 ml of acetylchloride is added thereto and the mixture is stirred for 1 hour. The mixture is added with ice and extracted with ether. The organic layer is washed with water and dried and concentrated to distill the solvent to give 167 mg (Yield: 93.4%) of 4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylamino)pyrimidine-5-carbardehyde. Thus obtained aldehyde compound is reacted in the same manner as in Example 1 (3)–(5) to give methyl 7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-acetyl-N-methylaminopyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenate (I b-2).

NMR ($CDCl_3$)δ: 1.27 (d, J=7,6H); 1.54 (m, 2H); 2.48 (d, J=6,2H); 2.52 (s, 3H); 3.39 (hept, J=7, 1H); 3.60 (s, 3H); 3.58 (brs, 1H); 3.74 (s, 3H): 4.21 (m, 1H); 4.48 (m, 1H); 5.50 (dd, J=5,16, 1H); 6.66 (dd, J=2,16); 7.11 (m, 2H); 7.61 (m, 2H).

(3) The thus obtained compound (I b-2) is reacted in the same manner as Example 1 (6) to give the objective compound (I a-2).

(Ia-2)



NMR ($CDCl_3$)δ: 1.27 (d, J=7,6H); 1.57 (m, 2H): 2.17 (s, 3H); 2.27 (d, J=6,2H); 3.72 (s, 3H); 3.50 (hept, J=7, 1H); 3.70 (m, 1H); 4.35 (q, J=6,1H); 5.59 (dd, J=5,16, 1H); 6.54 (d, J=16, 1H); 7.24 (m, 2H): 7.59 (m, 2H).

EXAMPLE 3–6

As a starting material, each pyrimidine carboxylate (III) obtained in Reference Example 1–3 is reacted in the same manner as Example 1 or 2 to give the compound (I b) and (I a). Their physical constants are shown in Table 1–3.

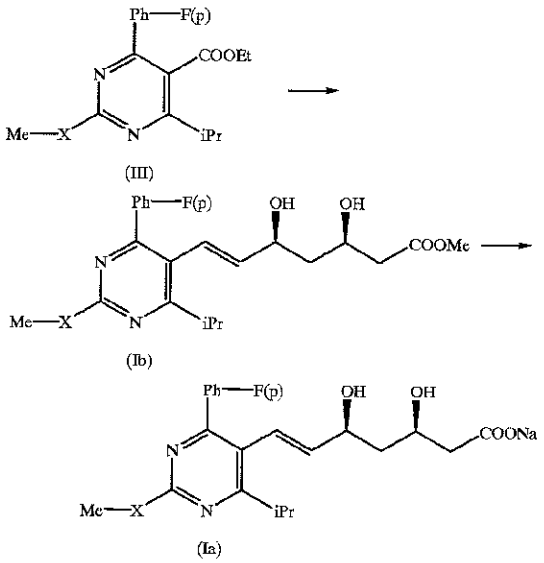


TABLE 1

Ex. No.	Startup material	Product NMR δ
3	(III-1)	1b-3(X: S)Yield 96.0% ($CDCl_3$, 1.26(d, J = 7.6H): 1.52(m, 2H): 2.47(d, J = 6, 2H): 2.60(s, 3H): 3.33(hept, J = 7, 1H): 3.73 (s, 3H): 4.18(m, 1H): 4.44(m, 1H): 5.44(dd, J = 5, 16, 1H): 6.60(dd, J = 2, 16, 1H), 7.07(m, 2H): 7.58(m, 2H) 1a-3(X: S)Yield 87.3% (D_2O) 1.20(d, J = 7, 6H): 1.47(m, 1H): 1.61(m, 1H): 2.26(m, 2H), 2.54(s, 3H): 3.36(hept, J = 7, 1H):

TABLE 1-continued

		3.71(m, 1H): 4.29(m, 1H): 5.43(dd, J = 6, 16, 1H): 6.55(d, J = 16, 1H): 7.16(m, 2H), 7.47 (m, 2H)
4	(III-2)	1b-4(X: SO_2): Yield 93.7% ($CDCl_3$) 1.31(d, J = 7, 6H): 1.52(m, 2H): 2.48(d, J = 6, 2H): 3.40(s, 3H); 3.47(hept, J = 7, 1H); 3.74 (s, 3H): 3.87(brs, 1H): 4.23(m, 1H): 4.49 (m, 1H); 5.59(dd, J = 5, 16H, 1H); 6.74(d, d, J = 2, 16, 1H); 7.12(m, 2H): 7.69(m, 2H) 1a-4(X: SO_2): Yield 70.9% (D_2O) 1.27(d, d, J = 7, 2, 6H); 1.60(m, 2H); 2.25(J = 6, d, 2H): 3.44(s, 3H): 3.51(hept, J = 7, 1H): 3.70(m, 1H): 4.33(q, J = 6, 1H): 5.65(d, d, J = 5, 16, 1H): 6.71(d, J = 16, 1H): 7.23(m, 2H); 7.60 7.60(m, 2H)

TABLE 2

Ex. No.	Starting material	Product NMR δ
5	(III-5)	1b-5(X: O): ($CDCl_3$) 1.27(d, 6H, J = 6.6 Hz): 1.35–1.68(m, 2H): 2.47 (m, 2H): 3.34(m, 1H): 3.78(s, 3H): 4.03(s, 3H): 4.19(m, 1H); 4.43(m, 1H): 5.43(dd, 1H, J = 5.6, 16 Hz): 6.59(dd, 1H, J = 1.4, 16 Hz): 7.03–7.64(m, 4H) 1a-5(X: O) Yield 57.7% ($CDCl_3$, CD_3OD) 1.27(d, 6H, J = 6.6 Hz): 1.35–1.68(m, 2H): 2.17–2.43(m, 2H): 3.36(m, 2H), 4.05(s, 3H): 4.37 (m, 2H): 5.48(dd, 1H, J = 5.6, 16 Hz): 6.54(dd, 1H, J = 1.4, 16 Hz): 7.06–7.65(m, 4H)
6	(III-4)	1b-6(X: N—SO_2NMe_2): ($CDCl_3$) 1.26(d, 6H, J = 6.6 Hz); 1.38–1.62(m, 2H): 2.47 (d, 2H, J = 5.8); 2.84(s, 6H), 3.35(m, 1H): 3.64(s, 3H); 3.74(s, 3H); 4.20(m, 1H): 4.44 (m, 1H); 5.42(dd, 1H, J = 5.4, 16 Hz): 6.60 (dd, 1H, J = 1.2, 16 Hz): 7.03–7.64(m, 4H) 1a-6: Yield: 91.2% ($CDCl_3$, CD_3OD) 1.26(d, 6H, J = 6.6 Hz); 1.36–1.69(m, 2H): 2.15–2.50(m, 2H); 2.85 (s, 6H); 3.41(m, 2H): 3.64 (s, 3H): 4.04(m, 1H): 4.37(m, 1H); 5.48 (dd, 1H, J-5.6, 16 Hz): 6.54(dd, 1H, J-1, 16 Hz): 7.05–7.66(m, 4H)

TABLE 3

Ex. No.	Starting material	Product NMR δ
7	(III-6)	1b-7(X: N—$NHSO_2Me$): Yield: 87.8% ($CDCl_3$) 1.24(d, J = 7, 6H): 1.51(m, 2H): 2.47(d, J = 6, 2H); 2.95(s, 3H); 3.35(hept, J = 7, 1H); 3.46 (d, J = 2, 1H): 3.55(s, 3H); 3.66(d, J = 2, 1H): 3.74 (s, 3H): 4.18(m, 1H): 4.44(m, 1H): 5.41 (dd, J = 5, 16, 1H); 6.58(dd, J = 2, 16, 1H); 7.09(m, 2H); 7.58(m, 2H), 7.70(s, 1H) 1a-7(X: N—$NHSO_2Me$): Yield: 74.7% (D_2O) 1.23(d, J = 7, 6H): 1.51(m, 2H): 2.26(d, J = 6, 2H) 3.10(s, 3H); 3.37(hept, J = 7, 1H): 3.44 (s, 3H): 3.70(m, 1H). 4.29(q, J = 6, 1H): 5.39 (dd, J = 5, 16, 1H): 6.58(d, J = 16, 1H): 7.19(m, 2H):7.52(m, 2H)

EXAMPLE 7

Calcium salt of the compound (I a-1) (sodium salt) 1.50 g (3.00 mmol) is dissolved in 15 ml of water and stirred at room temperature under nitrogen atmosphere, successively 3.00 ml (3.00 mmol) of 1 mol/L calcium chloride 3.00 ml (3.00 mmol) is added dropwise thereto over 3 minutes. The reaction mixture is stirred at the same temperature for 2 hours, and the resulting precipitate is collected, washed with water and dried to give 1.32 g of calcium salt as powdery. This compound started to melt at a temperature of 155° C., but the definitive melting point is ambiguous.

[α]D=+6.3° ±0.2° (C=2.011, 25.0° C., MeOH).

Anal Calcd. (%) for $C_{22}H_{27}N_3O_6SF$. 0.5Ca . $0.5H_2O$: C,51.85; H,5.53; N,8.25; F,3.73; Ca,3.93. Found: C,51.65; H,5.51; N,8.47; F,3.74; Ca,4.07.

Biological Activity

Experiment

The HMG-CoA reductase inhibitory effect

(1) Preparation of rat liver microsome

Sprague-Dawley rats, which were in free access to ordinary dietes containing 2% cholestyramine and water for 2 weeks, were used for the preparation of rat liver microsome. The thus obtained microsome was the purified according to the manner by Juroda et al., Biochem. Biophys. Act, 486, 70 (1977). The microsomal fraction obtained by centrifugation at 105,000×g was washed once with a buffered solution containing 15 mM nicotinamide and 2 mM magnesium chloride (in a 100 mM potassium phosphate buffer, pH 7.4). It was homogenized with a buffer containing nicotinamide and magnesium chloride at the same weight as the liver employed. The thus obtained homogenate was cooled down and kept at −80° C.

(2) Measurement of the HMG-CoA reductase inhibitory activities

The rat liver microsome sample (100 μl), which was preserved at −80° C., was fused at 0° C. and diluted with 0.7 ml of a cold potassium phosphate buffer (100 mM, pH7.4). This was mixed with 0.8 ml of 50 mM EDTA (buffered with the aforementioned potassium phosphate buffer) and 0.4 ml of 100 mM dithiothreitol solution (buffered with the aforementioned potassium phosphate buffer), and the mixture was kept at 0° C. The microsome solution (1.675 ml) was mixed with 670 μl of 25 mM NADPH (buffered with the aformentioned potassium phosphate buffer), and the solution was added to the solution of 0.5 mM [3^{-14}](HMG-CoA (3mCi/mmol). A solution (5 μl) of sodium salt of the test compound dissolved in potassium phosphate buffer is added to 45 μl of the mixture. The resulting mixture was incubated at 37° C. for 30 minutes and cooled. After termination of the reaction by addition of 10 μl of 2N·HCl, the mixture was incubated again at 37° C. for 15 minutes and then 30 μl of this mixture was applied to thin-layer chromatography of silica gel of 0.5 mm in thickness (Merck AG, Art 5744). The chromatograms were developed in toluene/acetone (1/1) and the spot, whose Rf value was between 0.45 to 0.60, were scraped. The obtained products were put into a vial containing 10 ml of scintillator to measure specific radio-activity with scintillation counter. The activities of the present compounds are shown in Table 4 as comparative ones based on the assumption that the activity of Mevinolin (sodium salt) as reference drug is 100.

TABLE 4

Test Compound	HMG-CoA reductase inhibitory activities
1a-1	442
1a-3	385
1a-5	279

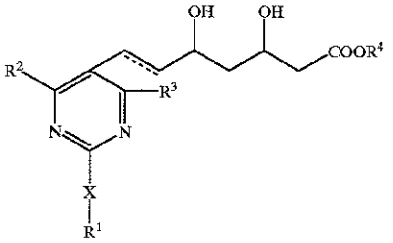
TABLE 4-continued

Test Compound	HMG-CoA reductase inhibitory activities
1a-7	260
Mevinolin Na	100

From the test data, the compounds of the present invention exhibit HMG-CoA reductase inhibition activities superior to Mevinolin.

What is claimed is:

[1. A compound represented by the formula (I):



wherein

R^1 is (1) lower alkyl which may have 1 to 3 substitutents independently selected from the group consisting of halogen, amino, and cyano, (2) C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano, or (3) C_1 to C_5 lower alkyl substituted by C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently sel-ected from the group consisting of lower alkyl, halo-gen, amino, and cyano; R^2 and R^3 each is independently (1) hydrogen, (2) lower alkyl which may have 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano, or (3) C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano; R^4 is (1) hydro-gen, (2) lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; X is sulfur, oxygen, or sulfonyl, or imino which may be substituted by formyl, acetyl, propionyl, butyryl, isobutyryl, vale-ryl, isovaleryl, amino substituted by sulfonyl or alkyl-sulfonyl, and sulfonyl substituted by alkyl, amino or alkylamino, the dotted line represents the presence or absence of a double bond, or the corresponding ring-closed lactone.]

[2. The compound claimed in claim 1, wherein X is imino which may be substituted by formyl, acetyl, pro-pionyl, butyryl, isobutyryl, valeryl, isovaleryl, amino substituted by sulfonyl or alkylsulfonyl, or sulfonyl substituted by alkyl, amino or alkylamino.]

[3. The compound claimed in claim 2, wherein X is imino which may be substituted by formyl, acetyl, pro-pionyl, butyryl, isobutyryl, valeryl, isovaleryl, alkylsul-fonylamino, or alkylsulfonyl.]

[4. The compound claimed in claim 1 having the (3R, 5S)-dihydroxy configuration.]

[5. A pharmaceutical composition comprising an ef-fective amount of the compound claimed in claim 1 as an active ingredient, in combination with a pharmaceu-tical excipient.]

6. The compound 7-(4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidin-5-yl)-(3R,5S)-dihydroxy-(E)-6-heptenoic acid in the form of a non-toxic pharmaceutically acceptable salt thereof.

7. The compound of claim 6 in the form of a sodium salt.

8. The compound of claim 6 in the form of a calcium salt.

* * * * *

EXHIBIT 3

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IN ITS
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EXHIBIT 4

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IN ITS
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EXHIBIT 5

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IN ITS
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EXHIBIT 6

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EXHIBIT 7

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EXHIBIT 8

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IN ITS
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EXHIBIT 9

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EXHIBIT 10

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EXHIBIT 11

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EXHIBIT 12

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EXHIBIT 16

REDACTED
IN ITS
ENTIRETY

EXHIBIT 17

07/897793

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/897,793	06/12/92	HIRAI	K 256586332

FORD, J

WENDEROTH, LIND & PONACK
SOUTHERN BUILDING
SUITE 700
805 FIFTEENTH STREET, N.W.
WASHINGTON, DC 20005

ART UNIT 1202

PAPER NUMBER 2

COMMISSIONER OF PATENTS AND TRADEMARKS

09/02/92

☐ This application has been examined ☒ Responsive to communication filed on 06/12/92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire THREE month(s), _____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1 - 8 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1 - 8 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☒ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☒ not been received
    ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

SEP - 4 1992

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

The claims in the application are claims 1-8.

Claim 1 is rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Note aryl and aralkyl appear in the claims variously. The definition of aryl is varied, note the different definitions in the footnotes of In re Sus, 134 USPQ 301. What do applicants intend? The claim need refect what is being claimed.

(B) The expression "each of which may have one or more substituents" does not say what the substituents, in this compound claim, are.

(C) When one says "or the corresponding ring closed lactone" which lactone does applicants have in mind? One formed between $-\overset{O}{\overset{\|}{C}}-OR^4$ and $X-R^1$?

Claims 2-4 are rejected as a result of being dependent on a rejected claim, but not for reasons peculiar to themselves.

Claim 5, on the other hand, is rejected under 35 USC 112, for the reasons noted in claim 1, as the substituents are not listed in the claim.

Claim 6 is rejected under 35 USC 112, first and second paragraphs.

(A) The term "aryl" reads on the residue of all acids, and is therefore, unsupported, and requires specific conception by the reader. Is lower alkanoyl intended?

(B) Alkyl is not limited from infinity in the claim.

Claim 7 is rejected under 35 USC 112. What optically active form do applicants have in mind, around what center?

Claim 8 is rejected as being non-statutory.

Claim 8 is not a proper method or composition claim,

Claim 8 is not properly distinguished from claim 1 itself.

Any inquiry concerning this communication should be directed to examiner Ford at telephone number (703) 308-1235.

Ford:lb
September 01, 1992

JOHN M. FORD
PRIMARY EXAMINER
GROUP 120

EXHIBIT 18

REDACTED
IN ITS
ENTIRETY

EXHIBIT 19

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

07/897793

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
07/897,793	06/12/92	HIRAI	K 256-G6332

EXAMINER
FORD, J

ART UNIT	PAPER NUMBER
1202	5

DATE MAILED: 01/08/93

WENDEROTH, LIND & PONACK
SOUTHERN BUILDING
SUITE 700
805 FIFTEENTH STREET, N.W.
WASHINGTON, DC 20005

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☒ Responsive to communication filed on 12-2-92 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire THREE month(s), _____ days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 9 - - 13 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 9 - - 13 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☒ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☒ been received. ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

Applicants response of 12-2-92 is noted.

The claims in the application are claims 9-13.

Claims 9 and 10 are rejected under 35 U.S.C. § 112, first and second paragraphs, as the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 9 and 10 one finds toward the end of the claim "optionally substituted amino and substituted sulfonyl". What are the substituents?

This is a compound claim. The compound claimed must be set forth clearly and exactly in the claims.

It is assumed that this unknown amino or sulfonyl are not X members.

Consider claim 11, when one reads "the substituent is" one does not know to what these substituents are bonded.

Any claim not specifically rejected is rejected as being dependent on a rejected claim.

Do applicants feel claim 12 is a proper dependent claim?

It is assumed that 3R, 5S is the sterochemistry of the hydroxy groups. Are isomers provided for in claim 9?

In regard to applicants response to the previous inquiry as to the lactone ring formation, the question is: which hydroxyl group forms the lactone with the $-C^{1}-OR^{4}$, the 3R or the 5S?

Receipt is acknowledged of papers submitted under 35 U.S.C. § 119, which papers have been placed of record in the file.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Any inquiry concerning this communication should be directed to examiner Ford at telephone number (703) 308-1235.

Ford:lb
January 04, 1993

JOHN M. FORD
PRIMARY EXAMINER
GROUP 120

TO SEPARATE, HOLD TOP AND BOTTOM EDGES, SNAP–APART AND DISCARD CARBON

FORM PTO-892 (REV. 2-92)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED		07/897,743	1302	5
		APPLICANT(S) Hirai et al		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A						
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

*	R	Moore Ind. J. Gen. Chem. Soc. Vol 107, pp 3694–3701 (1985)
	S	
	T	
	U	

EXAMINER	DATE	
J M Ford	12-31-92	* applicant's application

* A copy of this reference is not being furnished with this office action. (See Manual of Patent Examining Procedure, section 707.05 (a).)

EXHIBIT 20

REDACTED
IN ITS
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EXHIBIT 21

REDACTED
IN ITS
ENTIRETY

EXHIBIT 22

REDACTED
IN ITS
ENTIRETY

EXHIBIT 23

REDACTED
IN ITS
ENTIRETY

EXHIBIT 24

REDACTED
IN ITS
ENTIRETY

EXHIBIT 25

PTO/SB/52 (12-97)
Approved for use through 9/30/00. OMB 0651-0033
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

REISSUE APPLICATION DECLARATION BY THE ASSIGNEE	Docket Number (Optional) 256-G8332-RSU

I hereby declare that:
My residence, post office address and citizenship are stated below next to my name.

I am authorized to act on behalf of the following company: Shionogi Seiyaku Kabushiki Kaisha, and the title of my position with said company is: Representative Director.

The entire title to the patent identified below is vested in said company.

Name of Patentee(s):
Kentaro HIRAI; Teruyuki ISHIBA; Haruo KOIKE; and Masamichi WATANABE.

Patent Number	Date Patent Issued
5,260,440	November 9, 1993

Title of Invention
PYRIMIDINE DERIVATIVES

I believe said patentee(s) to be the original, first and sole or joint inventor(s) of the subject matter which is described and claimed in said patent, for which a reissue patent is sought on the invention entitled PYRIMIDINE DERIVATIVES, the specification of which

[X] is attached hereto.
[ ] was filed on _____ as reissue application number _____ and was amended on _____ (if applicable).

I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

I hereby claim priority benefits under 35 USC 119 of any application(s) for patent or inventor's certificate listed below and have also identified below any application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Country	Application No.	Date of Filing	Priority Claimed
Japan	188015/1991	July 1, 1991	YES

I hereby claim the benefit under 35 USC 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information material to patentability as defined in 37 CFR 1.56

(REISSUE APPLICATION DECLARATION BY THE ASSIGNEE, page 2)

Docket Number (Optional)
256-G6332-RSU

which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	U.S. Filing Date	Status
N/A	N/A	N/A

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

- [ ] by reason of a defective specification or drawing.
- [X] by reason of the patentee claiming more or less than he had the right to claim in the patent.
- [ ] by reason of other errors.

An error upon which the reissue is based is as follows:

Patentee claimed more than he had a right to claim by reason of the disclosure of European Patent Application 0 357 895, published May 16, 1990. The amended claims of the reissue application are considered to fully overcome any grounds for unpatentability based upon this reference.

All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant.

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connection therewith.

V. M. Creedon, Reg. No. 17,111; John T. Miller, Reg. No. 21,120; John T. Fedigan, Reg. No. 24,347; Michael R. Davis, Reg. No. 25,134; Matthew M. Jacob, Reg. No. 25,154; Jeffrey Nolton, Reg. No. 26,408; Warren M. Cheek, Jr., Reg. No. 33,367; Nils Pedersen, Reg. No. 33,145; and Charles R. Watts, Reg. No. 33,142.

Correspondence Address: Direct all communications about the application to:

WENDEROTH, LIND & PONACK, L.L.P.
2033 K Street, N.W.
Suite 800
Washington, D.C. 20006

Phone: (202) 721-8200
Fax: (202) 721-8250

(REISSUE APPLICATION DECLARATION BY THE ASSIGNEE, page 3)

Docket Number (Optional): 256-G6332-RSU

I hereby authorize the U.S. attorneys named herein to accept and follow instructions from Shionogi & Co., Ltd. as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and myself. In the event of a change in the persons from whom instructions may be taken, the U.S. attorneys named herein will be so notified by me.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 USC 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.

Full name of person signing (given name, family name)
Yoshihiko SHIONO

Signature: X Yoshihiko Shiono X

Date: SEP. 10. 1998

Residence: Osaka, Japan

Country of Citizenship: Japan

Post Office Address
1-8, Doshomachi 3-chome, Chuo-ku, Osaka 541, Japan

EXHIBIT 26

#3
10/21/98
SM

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEE FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Reissue application of	:	
Kentaro HIRAI et al.	:	
Serial No. [NEW]	:	[Examiner J. Ford
Filed August 27, 1998	:	Group Art Unit 1202]
PYRIMIDINE DERIVATIVES (Reissue application of Patent No. 5,260,440, issued November 9, 1993)	:	

INFORMATION DISCLOSURE STATEMENT

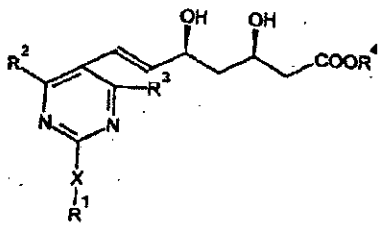
Assistant Commissioner for Patents
Washington, DC 20231

Sir:

Attached is form PTO-1449 listing the enclosed documents. This Information Disclosure Statement is being filed before the mailing date of the first Official Action on the merits, and therefore, no certification under 37 CFR 1.97(e) or fee under 37 CFR 1.17(p) is required. While this Information Disclosure Statement is not based on an exhaustive search, it is intended to be in full compliance with the rules. Should the Examiner find any part of its required content to have been omitted, prompt notice to that effect is earnestly solicited, along with additional time under Rule 97(f) to enable applicants to fully comply.

Applicants wish to make the following comments with respect to certain of the listed documents which were not before the Examiner during prosecution of original U.S. Patent 5,260,440.

The invention claimed in this reissue application is directed to certain pyrimidine derivatives and pharmaceutical compositions thereof. Compounds within the scope of the claims have been found useful for the inhibition of HMG-CoA reductase, which plays a major role in the synthesis of cholesterol. The compounds as presently claimed in this reissue application have the structure of formula (I) as follows:



wherein

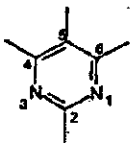
R^1 is (1) lower alkyl which may have 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano, (2) C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano, or (3) C_1 to C_6 lower alkyl substituted by C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano;

R^2 and R^3 each is independently (1) hydrogen, (2) lower alkyl which may have 1 to 3 substituents independently selected from the group consisting of halogen, amino, and cyano, or (3) C_6 to C_{12} aromatic group which may have 1 to 3 substituents independently selected from the group consisting of lower alkyl, halogen, amino, and cyano;

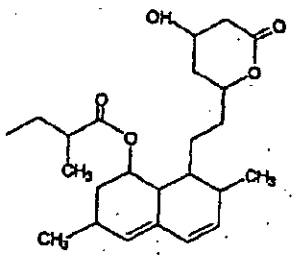
R^4 is (1) hydrogen, (2) lower alkyl, or a cation capable of forming a non-toxic pharmaceutically acceptable salt; and

X is imino which is substituted by formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, amino substituted by sulfonyl or alkyl-sulfonyl, or sulfonyl substituted by alkyl, amino or alkylamino.

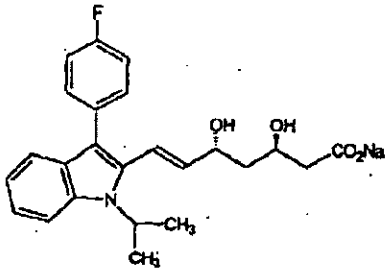
For consistency of reference herein, the positions of the pyrimidine ring will be numbered as follows:



The "Prior Art" section under "Background of the Invention" in the original and present specification (column 1, lines 9 to 20) discusses several known drugs that inhibit the activity of HMG-CoA reductase, which drugs are useful for the treatment of atherosclerosis. Early such compounds are represented by Mevinolin (U.S. Patent 4,231,938) having the following structural formula:



and later developed compounds, such as Fluvastatin (GB Patent 2,202,846) having the structural formula:



One direction of the art, as here pertinent, and as represented by the references discussed below, was the development of new central heterocyclic rings, including pyridine and pyrimidine rings, and the substituents thereon.

Applicants wish to make the following observations with respect to certain of the attached references, which will be considered in approximately the order of their respective dates.

A. U.S. 4,868,185 (Chucholowski et al.), filed December 10, 1987 and issued September 19, 1989;

B. U.S. 5,925,852 (Kesseler et al.), filed July 8, 1988 and issued May 15, 1990;

C. U.S. 5,026,708 (Fujikawa et al.), filed September 12, 1988 and issued June 25, 1991;

D. EPA 0 330 057 (Fey et al.), published August 30, 1989 (Australian AU-A-30202/89 provided as a corresponding English language application);

E. EPA 0 367 895 (Kathawala), published May 16, 1990;

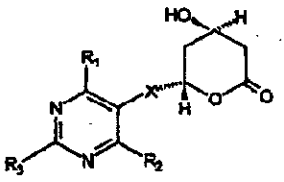
F. G. Beck et al., J. Med. Chem., 33, 52-60 (1990); and

G. B. Roth et al., J. Med. Chem., 34, 463-466 (1991).

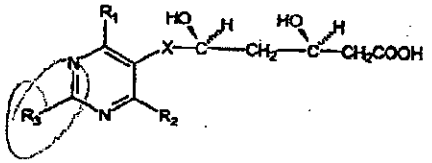
References A-E are presented as disclosing chemical structures similar to those disclosed in the presently claimed application. References F and G are cited as showing teaching in the art with respect to the relationship between the chemical structure and biological activity of certain HMG-CoA reductase inhibitors, particularly with respect to lipophilicity and overall CLOGP values, at a time just prior to the present invention.

A. U.S. 4,868,185 (Chucholowski et al.)

U.S. 4,868,185 (hereinafter "Chucholowski") was filed December 10, 1987 and issued on September 19, 1989. This reference discloses certain trans-6-[[(substituted)-pyrimidine-5-yl]ethyl - and ethenyl]tetrahydro-43-hydroxypyran-2-ones and the corresponding dihydroxy ring-opened acids, which are said to be potent inhibitors of HMG-CoA reductase, and useful in lowering blood serum cholesterol levels. The compounds are of the general formula:



wherein X is $-CH_2CH_2-$ or $-CH=CH-$ (preferably in the trans configuration), and the corresponding dihydroxy ring-opened acids are of the general formula:



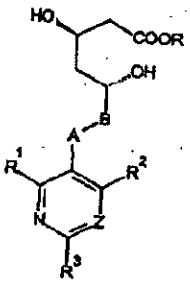
R_1 and R_2 are independently selected from hydrogen; alkyl of from one to six carbons; alkoxy of from one to four carbon atoms; trifluoromethyl; cyclopropyl; cyclohexyl; cyclohexylmethyl; phenyl; phenyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms; phenylmethyl; or phenylmethyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms; and

R_3 is hydrogen; alkyl of from one to six carbon atoms; trifluoromethyl; cyclopropyl; phenyl; or phenyl substituted with fluorine, chlorine, bromine, hydroxy, trifluoromethyl, alkyl of from one to four carbon atoms, or alkoxy of from one to four carbon atoms.

Even in the broadest genus, there clearly is no overlap between the disclosure of the Chucholowski patent and the claims of this reissue application. More particularly, there is no possibility or suggestion of any heteroatom group in the 2-position (R_3) of the pyrimidine ring of Chucholowski, let alone the imino group recited in the present application. Instead, phenyl and substituted phenyl groups are stated as preferred for R_3, and only methyl and phenyl groups are exemplified in the 2-position. In contrast, the claimed compounds have an imino group directly attached in the R_3 position which is further substituted as disclosed.

B. U.S. 4,925,852 (Kesseler et al.)

U.S. 4,925,952 (hereinafter "Kesseler et al.") was filed July 8, 1988, issued May 15, 1990, and discloses a series of pyrimidine and pyridine derivatives said to be inhibitor of HMG-CoA reductase having the general formula:

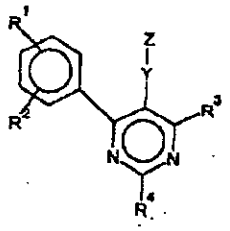


wherein Z is N or CH, and A–B is $-CH=CH-$ or $-CH_2-CH_2-$. Generically, each of R^1, R^2 and R^3 may be hydrogen, a saturated or unsaturated hydrocarbon with up to 6 carbon atoms, optionally bearing a saturated or unsaturated cyclic hydrocarbon of from 3 to 6 carbon atoms on the terminal carbon atom; a cyclic hydrocarbon from 3 to 7 carbon atoms, saturated or unsaturated once or twice; and an aromatic group selected from phenyl, furyl, thienyl and pyridyl which may be further substituted. The Examiner's attention is also called to the list of pyrimidinyl compounds at columns 10 to 13, wherein each 2-position substituent is a hydrocarbon, with or without further substitution. See also substituents identified as R^3 in Tables 1 to 14 of the specification. It will be seen that the exemplified 2-position substituents are limited to methyl, phenyl, dimethylphenyl, 4-fluorophenyl, isopropyl, t-butyl, cyclohexyl, ethyl and 4-hydroxyphenyl, and do not even vaguely suggest an imino or other N-linked group.

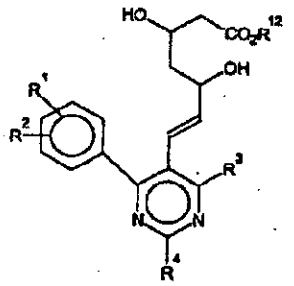
The compounds of the Kesseler et al. reference are therefore structurally unsuggestive of the compounds claimed in the present reissue application, wherein substituent on the 2-position of the pyrimidine ring is a nitrogen link X to group R^1.

C. U.S. 5,026,708 (Fujikawa et al.)

U.S. 5,026,708 (hereinafter "Fujikawa et al.") was filed on September 12, 1988 and issued June 25, 1991. The Fujikawa reference discloses "pyrimidine type mevalanonlactones", said to be useful as anti-hyperlipidemic, hypolipoproteinemic and anti-atherosclerotic agents. The Fujikawa et al. compounds have the following basic structure:

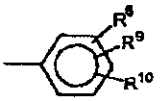


with various disclosed moieties for R^1, R^2, R^3, R^4, Y and Z. In particular, Table 1 at columns 12 to 16 of Fujikawa et al. provides a number of examples of compounds which can be prepared as the acid or sodium salt (R^{12}) having the following formula:



with the various substituents for R^1, R^2, R^3 and R^4.

Each of the Examples is structurally unsuggestive of the compounds claimed in the present reissue application, and there is no generic overlap. In particular, the permissible substituents at the 2-position of the pyrimidine ring (R^4) are limited to C_{1-6} alkyl, C_{3-7} cycloalkyl, α- or β-naphthyl, 2-, 3- or 4-pyridyl, or an optionally substituted phenyl represented by

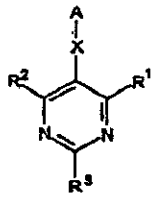


wherein R^8, R^9 and R^{10} are as defined in column 2, line 45 through column 3, line 10. Each R^4 substituent is carbon-linked to the pyrimidine ring, in contrast to the imino group X of all compounds claimed in the present reissue application. In the compounds exemplified in Fujikawa et al., the 2-position substituents are all phenyl, substituted phenyl, pyridyl, cyclohexyl, naphthyl, t-butyl or hexyl.

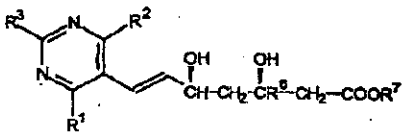
D. EPA 0 330 057 (Fey et al.)

European Patent Application No. 0 330 057 (hereinafter "Fey et al.") was published August 30, 1989, and generically discloses a broad range of substituted pyrimidines, said to have a good inhibitory action on HMG-CoA reductase. Inasmuch as Fey et al. is in German, a copy of the English-language Australian Patent Application AU-A-30202/89 has been provided. The Australian patent application is understood to correspond to the German-language European application, and will be referred to herein.

The Fey et al. reference broadly discloses a generic range of substituted pyrimidines having the general formula:



wherein each of X, A, R^1, R^2 and R^3 may be a vast array of substituents which can be combined in countless combinations and permutations, as well as in a variety of isomeric forms. Among the various isomeric forms depicted at pages 19 and 20 is the following structure:

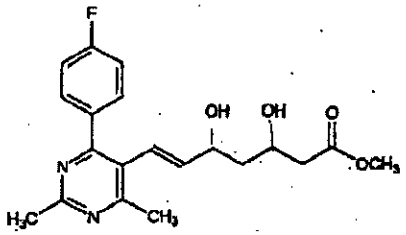


An NR^4R^5 group is generically listed as a substituent at the 2-position of the pyrimidine ring (R^3 in the Fey et al. disclosure) (pages 2-3), along with the disclosure of thousands of other substituents at the R^3 position. Even the "particularly preferred" embodiment of the Fey et al. reference generically includes at least an estimated 10^{15} compounds, when one considers the possible combinations of these various R^3 substituents together with the numerous substituents identified for each of the other variables of this embodiment. The Fey et al. reference does not include the NR^4R^5 substituent in the most preferred embodiment, in which:

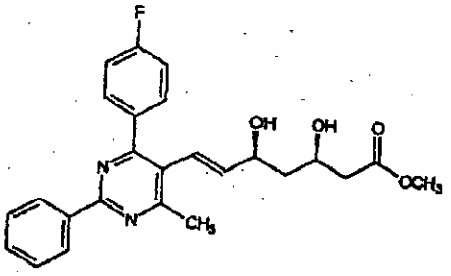
> R^3 stands for methyl, isopropyl, tert.-butyl or
> for phenyl which can be monosubstituted or disubstituted by identical or different methyl, methoxy, fluorine or chlorine.

This clear preference is confirmed by the Examples (of which there are only three within the general structure), where, in each instance, the R^3 substituent is a methyl or a phenyl group. The remaining Examples disclose intermediates, not final products. For instance, the following structures are illustrated in the Fey et al. Examples:

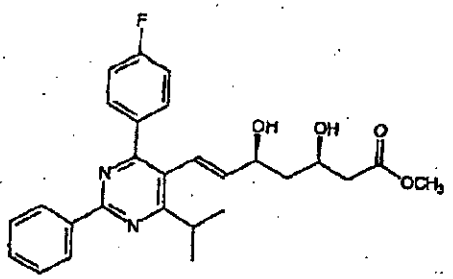
Example 8



Example 15



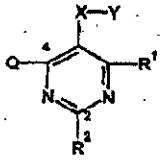
Example 23



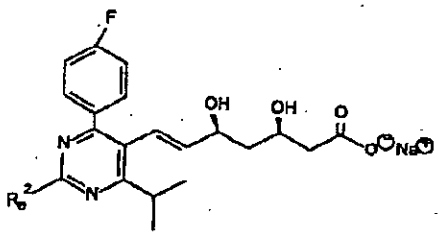
These preferred and exemplified compounds of the Fey et al. reference are structurally unsuggestive of the compounds claimed in the present reissue application, which require an imino group linked to the pyrimidine ring at the 2-position.

E. EPA 0 367 895 (Kathawala)

EPA 0 367 895 (hereinafter "Kathawala") was published on May 16, 1990. It is directed toward certain pyrimidinyl-substituted hydroxyacids, lactones and esters, said to be cholesterol biosynthesis inhibitors and, as such, useful in the treatment of hypolipoproteinemia and anti-atherosclerosis. Kathawala discloses a broad genus of compounds of formula I:



with the variables as set out on pages 2 to 3 of the specification. A wide range of permissible substituents at the 2-position of the pyrimidine ring (R^2) is itemized from page 2, line 21 through page 3, line 18. None of the generically disclosed 2-position substituents of Kathawala include any of the 2-position substituents of the present reissue claims, and are quite structurally unsuggestive thereof. In this regard, Kathawala discloses at page 9 as one "especially preferred embodiment" of the invention, compounds of the formula:

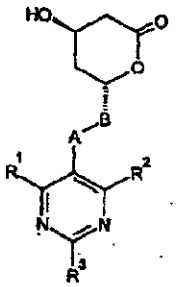


wherein R_6^2 is dimethylamino or 4-morpholinyl. The dimethylamino and 4-morpholinyl compounds are exemplified in Examples 1 and 2, respectively. However, the 2-position substituent in the bulk of the remaining examples 2 to 9, 10(a-g) and 11(a-i) is selected from alkyl or phenyl groups, specifically phenyl, isopropyl, t-butyl and methyl.

F. <u>The Beck et al. and Roth et al. Publications</u>

The Beck et al. publication, published in 1990, conducts a structure/activity investigation to determine the effect of the nature of the substituent at the 2-position of the pyridine and pyrimidine rings on HMG-CoA reductase inhibition,[1] with compounds having the generic formula:

[1] The Beck et al. publication uses a numbering system consistent with pyridine and therefore denominates as the 6-position what has been denominated herein as the 2-position, which will continue to be referred to as the 2-position herein.



2: A—B = (E)CH=CH
3: A—B = (Z)CH—CH
4: A—B = CH_2CH_2

In all cases, the R^3 substituent is a hydrocarbon. In no instance is the R^3 group attached to the pyrimidine ring through an imino group.

The Roth et al. publication, published in early 1991, investigates the relationship between tissue selectivity and lipophilicity for inhibitors of HMG-CoA reductase. The authors acknowledge the proposal that tissue selectivity may be influenced primarily by the relative lipophilicity of the drugs with the relatively more hydrophilic compounds showing higher liver selectivity. After comparing a series of compounds' tissue activity versus CLOGP, the report states:

> The results of this study support the hypothesis that tissue selectivity is determined primarily by lipophilicity and that an optimal CLOGP range (CLOGP 2-4) exists for inhibition of cholesterol biosynthesis in peripheral tissues, whereas liver does not discriminate compounds on the basis of lipophilicity below this optimum.

A copy of each of the above references is submitted herewith, and are listed on the attached Form PTO-1449. Consideration of the foregoing and enclosures, and the return of a copy of the attached Form PTO-1449 with the Examiner's initials in the left column per MPEP 609, are respectfully solicited.

Respectfully submitted,

Kentaro HIRAI et al.

By _____
Matthew Jacob
Registration No. 25,154
Attorney for Applicants

MJ/adc
Washington, D.C.
Telephone (202) 721-8200
August 27, 1998

#3

Sheet 1 of 1

FORM PTO 1449 (modified)

U.S. DEPARTMENT OF COMMERCE
PATENT AND TRADEMARK OFFICE

LIST OF REFERENCES CITED BY APPLICANT(S)
(Use several sheets if necessary)

Date Submitted to PTO: August 27, 1998

ATTY DOCKET NO. 256-G6332-RSU

SERIAL NO. [NEW] 09/141,231

APPLICANT Kentaro HIRAI et al.

FILING DATE August 27, 1998

GROUP ~~1202~~ 1614

U.S. PATENT DOCUMENTS

*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	AA	4,868,185	9/1989	Chucholowski et al.	514	256	
	AB	4,925,852	5/1990	Kesseler et al.	514	256	
	AC	5,026,708	6/1991	Fujikawa et al.	514	256	
	AD						
	AE						
	AF						
	AG						
	AH						
	AI						

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	AJ	0 330 057	8/1989	Europe			X	
	AK	0 367 895	5/1990	Europe				
	AL							
	AM							
	AN							

OTHER DOCUMENT(S) (Including Author, Title, Date, Pertinent Pages, Etc.)

AO	G. Beck et al., J. Med. Chem., 33, 52-60 (1990).
AP	B. Roth et al., J. Med. Chem., 34, 463-466 (1991).
AQ	

EXAMINER [signature] DATE CONSIDERED 8-1-98

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.